REVIEW ARTICLE

Pancreatic Enzyme Therapy

Joachim Mössner, Volker Keim

SUMMARY

Background: Treatment with pancreatic enzymes must be based on an understanding of the normal physiology and pathophysiology of exocrine pancreatic function, as well as of the diseases that cause exocrine pancreatic insufficiency of either a structural or a functional type. These include chronic pancreatitis, pancreatic cancer, cystic fibrosis, pancreaticocibal asynchrony after gastric or pancreatic surgery, and celiac disease.

Methods: Selective review of the literature.

Results: Exocrine pancreatic insufficiency can cause meteorism, diarrhea, steatorrhea, and weight loss. All of these manifestations are non-specific except steatorrhea. Enzyme supplementation is indicated only for the treatment of demonstrated pancreatic dysfunction; unfortunately, however, no sensitive and specific pancreatic function tests are currently available. As a result, pancreatic enzyme supplementation is considered to be indicated on pragmatic grounds when, for example, the patient is suffering from diarrhea and weight loss and has been demonstrated to have a disease leading to exocrine pancreatic insufficiency. To be acceptable for clinical use, a pancreatin preparation must satisfy the following criteria: it must be enterically coated, so that it will not be destroyed by gastric acid; mix well with gastric chyme; exit the stomach simultaneously with chyme; and be rapidly released from its enteric coating upon entering the duodenum. Although there have been no large-scale, randomized comparative studies of different types of pancreatin preparation, the current clinical preference is for enterically coated micropellets or minitablets with a diameter of 2 mm or less. The initial dosage is 20 000 to 40 000 units of lipase taken once or twice per meal, with dose adjustment afterward as needed. The dose can be raised, and a proton-pump inhibitor can be added on.

Conclusion: There is still no simple test that can be used to diagnose pancreatic exocrine insufficiency with certainty. The treatment is symptomatic; its goals are to lessen steatorrhea and reverse weight loss.

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Medizinische Klinik und Poliklinik für Gastroenterologie und Rheumatologie Department für Innere Medizin, Neurologie und Dermatologie: Prof. Dr. med. Mössner, Prof. Dr. med. Keim

The physiological processes that go on during food digestion are complex. This is particularly the case for the regulation of the secretion and activation of pancreatic enzymes. The causal chain begins with the acid leaving the stomach and entering the duodenum. This releases secretin, which stimulates volume secretion and the secretion of bicarbonate from the pancreas. The result of this is to alkalize the duodenum, producing an optimal pH environment for pancreatic enzymes (*Figure*). Stimulants of enzyme secretion are predigested nutritional elements such as peptones, and amino acids and fatty acids, which lead to release of cholecystokinin (CCK) by the duodenum. This induces contraction of the gallbladder and releases acetylcholine from intrapancreatic nerve fibers, which in turn stimulate enzyme secretion from the pancreas (*Figure*). CCK does not itself appear to have a direct effect on the human pancreas.

To prevent self-digestion of the organ, most pancreatic enzymes are synthesized as inactive precursors, so-called zymogens or proenzymes (trypsinogen, chymotrypsinogen, proelastase, etc.) and then additionally packaged in organelles (zymogen granules). Amylase is spontaneously active. Lipase has an intermediate status, being secreted as an active enzyme, but its lipolytic activity is tied to activation of a cofactor (colipase). The exocrine enzymes are released from the acinar cells of the pancreas via a complex mechanism (the membrane of the zymogen granules fuses with the apical membrane of the acinar cells). The process of activation of the proenzymes begins in the duodenum with secretion of enterokinase from the mucosa of the upper small intestine into the intestinal lumen. This results in the splitting off of a peptide (trypsinogen activation peptide, TAP) from trypsinogen, which leads via a complex folding process to the formation of active trypsin. Trypsin is now in a position to convey the remaining proenzymes into their active form (*Figure*).

The mechanisms for switching off exocrine pancreatic secretion are only partially understood. It is believed that when the chyme comes into contact with the ileum, hormones are released (e.g., PYY, peptide tyrosine tyrosine) that lead to inhibition of pancreatic secretion and at the same time to inhibition of appetite (1).

In various pancreatic diseases these very complex processes can become impaired. This review will discuss the pathophysiology of pancreatic insufficiency and the diagnosis and treatment of this disease complex. A selective literature search was carried out on Medline using the search terms "pancreas,"

"secretion," "chronic pancreatitis," and "exocrine insufficiency."

Etiology of exocrine pancreatic insufficiency

The most common cause of exocrine pancreatic insufficiency in adults is chronic pancreatitis, followed by pancreatic carcinoma, pancreatic resection, and defective healing after necrotizing acute pancreatitis with loss of pancreatic acini. In children, the most common cause is cystic fibrosis. Thanks to successful pneumological therapy, many patients with cystic fibrosis reach adult age with pancreatic insufficiency that continues to require treatment. Exocrine insufficiency also seems to be very common in diabetes mellitus. However, this is the subject of some controversy, in particular because it is difficult to understand how functionally relevant exocrine insufficiency could be present in patients with type II diabetes, who are usually overweight.

In addition to the organic causes of exocrine pancreatic insufficiency, there are functional causes. These include among others gluten-sensitive enteropathy, Crohn's disease with pronounced ileal involvement, and postcibal asynchrony. After pancreatic resection, both functional (i.e., postoperative) and organic causes may result in insufficiency (e.g., a small, chronically altered pancreatic remnant). After gastrectomy, even partial resection of the stomach, or gastroenterostomy (for morbid obesity or tumor-related duodenal stenosis), either the chyme enters the duodenum too soon or failure of the chyme to transit to the duodenum results in too little CCK and secretin being released. This pancreatic postcibal dyssynchrony explains functional digestive insufficiency. Since the problems associated with pancreatic surgery were described in a recently published review, we will not go into them here (2).

Chronic pancreatitis

In the industrialized nations, 70% to 80% of cases of chronic pancreatitis are regarded as alcohol-induced. In 20% to 30% of cases no triggering cause is identified. More rarely encountered causes are pancreas divisum, hyperparathyoidism, and pronounced hypertriglyceridemia. Genetic alterations are demonstrated in about 30% to 35% of patients, e.g., mutations of the CFTR (cystic fibrosis transmembrane conductance regulator), SPINK (serine protease inhibitor of the Kazal type), or chymotrypsin C (3). In fewer than 1% of cases hereditary pancreatitis, a disease with autosomal dominant transmission, is present. In 70% to 80% of these cases there are mutations of the cationic trypsinogen (4).

Many patients, however, have more than one risk factor, e.g., low alcohol consumption in addition to a genetic risk factor or nicotine abuse, and for this reason classification into just one category, e.g., "chronic alcoholic pancreatitis" is not meaningful. It would be more accurate to use the term "chronic pancreatitis" and list the existing risk factors.

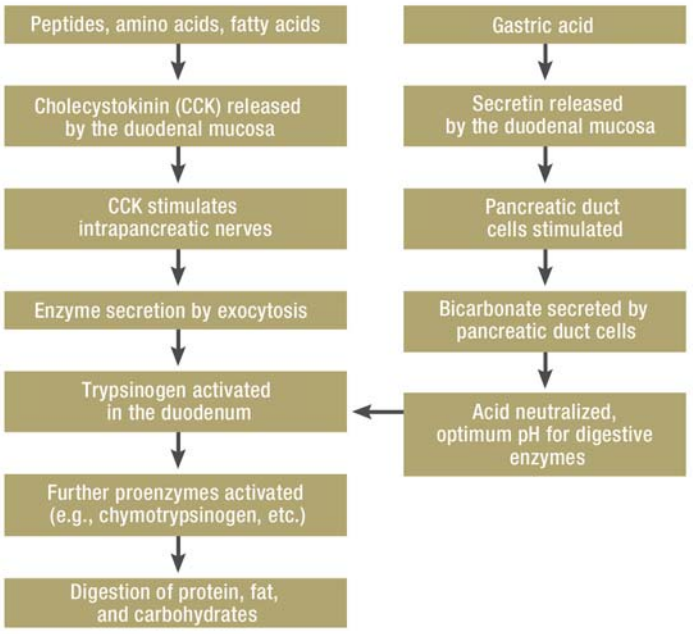
The time point at which maldigestion will occur is not predictable in chronic pancreatitis. The probability of exocrine insufficiency increases with the duration of the disease. After 10 years, more than half of patients with alcohol-associated chronic pancreatitis have exocrine insufficiency; at the end of 20 years almost all of them do (5). In non-alcohol-related pancreatitis the progression to exocrine insufficiency is slower (6).

The pancreas has a large reserve capacity. According to DiMagno et al., more than 90% of the organ must be destroyed before steatorrhea results. Steatorrhea is characterized by voluminous, yellowish, foul-smelling stool with a daily total stool weight of well over 200 g and the excretion of more than 7 g fat per day in the stool (7). Carbohydrate and protein digestion are partly accomplished by enzymes in the saliva (amylase), stomach (pepsin), and mucosa of the small intestine (peptidases, saccharidases). Fat digestion, however, is largely dependent on pancreatic lipase.

Pancreatic insufficiency after severe acute pancreatitis and in cancer of the pancreas

After severe acute pancreatitis or after pancreatic surgery, exocrine insufficiency can occur. The cause is the lack of exocrine tissue. Up until now, hypertrophy of the organ remnant has not been demonstrated after pancreatic resection. However, in patients with an isolated episode of, e.g., biliary pancreatitis, improvement of pancreatic function over the course of 12 to 24 months after the event is possible. This is in contrast to patients with chronic pancreatitis, in whom pancreatic function progressively deteriorates (5).

FIGURE



Physiological processes during food digestion

BOX

Tests to demonstrate exocrine pancreatic insufficiency

- Cholecystokinin secretin test
- Fecal elastase determination
- Mixed triglyceride breath test
- Fecal fat excretion
- Magnetic resonance cholangiography (MRC) after secretin stimulation
- Visual stool examination

Pancreatic insufficiency is also known in patients with cancer of the pancreas. In these patients it is due to obstruction of the pancreatic duct by the tumor, and is a contributory reason why these patients lose a lot of weight.

Diagnosing pancreatic insufficiency

Many procedures exist to show the presence of pancreatic insufficiency, based on a variety of underlying test principles (*Box*). The fact that there are so many examination techniques is an indication that none of them can show the presence of the disease reliably.

The most sensitive direct test of pancreatic function, the CCK secretin test, is no longer carried out in Germany, because CCK (formerly known as pancreozymin) and its synthetic analog ceruletide are no longer available for use in humans in Germany. Accurate, quantitative demonstration of the presence of pancreatogenic steatorrhea requires measurement of the fat excretion in the stool, which is determined in a three-day sample after a standardized diet with a known fat content (pathological level: >7 g per day). For understandable reasons, this procedure too is little used nowadays. Today, pancreatic insufficiency is usually shown by fecal elastase determination. However, a meta-analysis has shown that this procedure is only reliable in cases of moderately severe to severe pancreatic insufficiency (8). In patients with diarrhea of various causes, the fecal elastase concentration is often reduced to a false-positive level; it is possible that a special collecting vessel could help here (9). The mixed triglyceride breath test, an indirect test, has likewise not yet been sufficiently evaluated for sensitivity. In this test, triglycerides are labeled with the stable ^{13}C isotope. If enough lipase is present, ^{13}C-labeled CO_2 will be formed, which can be measured in the expired breath (10). Visual assessment of increased fat excretion is only possible, at best, in patients with severe steatorrhea (11). Indirect pancreatic function tests, such as the fluorescein dilaurate test and kinetic chymotrypsin determination, are no longer available in Germany. Neither does determination of serum lipase or amylase activity allow any conclusion about pancreatic function (12). Magnetic resonance cholangiography (MRC) after secretin stimulation has not been evaluated in large comparison studies as to its sensitivity in demonstrating pancreatic insufficiency. Whether an endoscopic secretin test (13) would be an improvement remains to be shown.

Chronic pancreatitis can be demonstrated with the aid of imaging techniques such as ultrasonography, endosonography, CT, and MRI. However, since there is no close correlation between the structure and the remaining function of the organ (14), sufficient secretion may in fact still be present despite the presence of (morphologically) extensive chronic pancreatitis with duct widening and calcifications. In almost all patients with morphologically severe organ destruction, however, loss of exocrine function may be assumed. Equally, if morphological changes are discreet, no or at worst only marginal exocrine insufficiency need be anticipated. Opinions in the literature vary about the significance of the additional presence of bacterial overgrowth of the gut (15).

Treatment of exocrine pancreatic insufficiency

Available enzyme preparations

Porcine pancreatin preparations are the most widely used (16). An overview of different preparations and their effectiveness has been published by Löhr et al. (17). The requirements for a pancreatin preparation are that it must have high lipase activity, protect the lipase from being destroyed by gastric acid, mix with the chyme and leave the stomach with it, and also rapid release of the pancreatin out of the protective enteric coating into the duodenum. Since the lipase of porcine pancreatin is destroyed by proteases and acids, it is necessary, in patients who retain the ability to secrete gastric acid, to protect the pancreatin from the influence of this acid. Other elements that are important for the effectiveness of an enzyme preparation are particle size (unimpeded gastric emptying) and the speed with which the enzymes are released in the duodenum. The best particle size is believed to be a diameter of ≤ 2 mm, since it is assumed that these particles can then exit the stomach at the same time as solid food (18). The enzymes should be released within 30 minutes. Reduced buffering of the gastric acid, due to low bicarbonate secretion in chronic pancreatitis, delays the release of the enzyme from the enteric-coated particles and thus impedes digestion. This may be one explanation why steatorrhea cannot usually be completely cured by even high-dose pancreatin substitution.

In one study, which due to low case numbers could only test for equivalence, we found that enteric-coated mini-micropellets (diameter 90% <1.25 mm) were equivalent to minipellets (diameter >70% >1.25 mm to 2.0 mm) in terms of improving fat digestion (19). Orally administered pancreatin preparations, if not enteric coated, are broken down not only by acid and

pepsin but also, after they are released into the duodenum, by the enzymes themselves, especially the lipase that is so important (20).

The state of published research into the use of fungal lipase preparations (rizolipase from *Rhizopus oryzae*) is unsatisfactory. From a theoretical point of view, an acid-stable microbiologically produced lipase should be ideal (21). However, to date this preparation has not been licensed for use in humans, and it has not been shown to be equipotent to porcine pancreatin in terms of fat digestion.

Indication for enzyme therapy and dosage

The indication for pancreatic enzyme therapy is exocrine insufficiency. As has been described, it is difficult to prove insufficiency and the findings are unreliable. For this reason, the criteria are that the patient does not only have a disease that leads to exocrine insufficiency but also shows symptoms such as meteorism, diarrhea, steatorrhea, and/or weight loss. The same is true for a patient with functional pancreatic insufficiency such as postcibal dissynchrony after gastric/pancreatic surgery or gluten-sensitive enteropathy.

Dosage of pancreatic enzyme preparations is individually tailored. A reasonable starting dose is 25 000 to 40 000 IU of lipase per main meal. The dosage for light meals or snacks depends on their size but should be at least 10 000 IU. To ensure that they are well mixed with the food in the stomach, pancreatin preparations should be taken not before but during or immediately after the meal (22). If the treatment is unsuccessful, the dose can be increased. If success remains elusive, co-medication with proton pump inhibitors (PPI) should be tried. Supplementary pancreatic enzymes should also be given to patients with severe exocrine insufficiency who are on polymeric diets (so-called astronaut food) (23).

In exceptional cases exocrine insufficiency may be present even when results of pancreatic function tests are non-pathological or borderline pathological. In such cases the enzymes may be given over the course of about 14 days. If no sustained improvement of the symptoms is seen, it is very likely that the problem is not exocrine insufficiency and the pancreatic enzymes should not be prescribed further.

Adverse effects

Inflammatory colonic stenoses have been reported as a side effect of high-dose pancreatin therapy in patients with cystic fibrosis (24). It is not known whether these stenoses were caused by ingredients in the enteric coating or by the high concentration of the digestive enzymes.

Conflict of interest statement
The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Exocrine pancreatic insufficiency must be shown to be present before pancreatic enzyme preparations are given.
- Since the sensitivity and specificity of indirect pancreatic function tests are very low, especially in cases of mild pancreatic insufficiency, the decision that pancreatic enzyme substitution is indicated is made empirically:
  - proven presence of disease that can lead to exocrine pancreatic insufficiency (chronic pancreatitis, organ defect after necrotizing pancreatitis, pancreatic cancer, cystic fibrosis, functional pancreatic insufficiency)
  - presence of meteorism, diarrhea, steatorrhea, weight loss
- Enteric-coated pancreatin should be given (minitablets of 2 mm diameter or micropellets of <2 mm diameter), 1–2 × 25 000 to 40 000 IU per main meal, 1 × 10 000 IU for snacks or light meals.
- If steatorrhea does not improve, increase the dosage and consider additional acid blockade with a proton pump inhibitor.

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Corresponding author
Prof. Dr. med. Joachim Mössner
Prof. Dr. med. Volker Keim
Medizinische Klinik und Poliklinik für Gastroenterologie und Rheumatologie
Department für Innere Medizin, Neurologie und Dermatologie
Universitätsklinikum Leipzig, AöR
Liebigstr. 20
04103 Leipzig, Germany
moej@medizin.uni-leipzig.de